ASENAPINE FOR THE TREATMENT OF SCHIZOPHRENIA IN A PATIENT WITH OVERWEIGHT OR PREDISPOSITION FOR OVERWEIGHT

The invention relates to a method for the treatment of schizophrenia with an antipsychotic agent administered to a patient with overweight.

The average human population is afflicted with a life-time occurrence of schizophrenia at a rate of about 0.5 - 1% (Goldber et al.; Canadian J. of Psychiatry Vol 47; pp 833-843; 2002). The disease, if untreated, is completely debilitating with regard to social and economic functioning of the afflicted person. Fortunately, considerable progress has been made during the last 45 years in the treatment of the disease, resulting in some social behaviour benefits for many patients. It is the use of effective anti-psychotic drugs that has produced this dramatic improvement in treatment outcome. With the classic antipsychotic agents, such as chlorpromazine, haloperidol, spiperone etc. the importance of dopamine receptor blockade as the mechanism of action for antipsychotic effects has been demonstrated. These drugs nevertheless had shortcomings which were the challenge to be overcome by new agents. These side effects, collectively referred to as extrapyramidal side (EPS) effects, are Parkinson-like behaviour, akathisia, dystonias and serious, sometimes irreversible disturbances in muscle control, known as tardive dyskinesia (TD). Clozapine, an older drug showed that antipsychotic effects could be obtained without frequent inducement of the afore-mentioned side effects. This led to the class of atypical antipsychotic agents, which are those that are as effective as the first generation of antipsychotic drugs, but less prone to induce extrapyramidal side effects and having a broader therapeutic efficacy. The latter refers to efficacy against the negative symptoms of schizophrenia. The atypical anti-psychotic drugs can be further subdivided into three categories based upon receptor-binding profiles and the side effects that follow. These categories are (a) the relatively pure dopamine antagonists (D2 antagonists, including sulpiride and amisulpiride), (b) the dopamine (D2)-serotonin (5-HT_2)-norepinephrine (alpha 1) antagonists (risperidone, ziprazidone and sertindole) and (c) the multireceptor antagonists (clozapine, olanzapine and seroquel) (See Gerlach and Peacock, International Clinical Psychopharmacology 10 Suppl 3: 39-48, 1995.; Tamminga and Lahti, International Clinical Psychopharmacology 11 Suppl 2: 73-76, 1996). These atypical antipsychotics, however, cause substantial weight gain that is both greater than conventional antipsychotics and of clinically meaningful magnitude. This leads in individual cases to poor compliance and other adverse health effects. The largest weight gains are associated with clozapine and olanzapine, and the smallest with quetiapine and ziprasidone. Risperidone is associated with modest weight changes that are not dose

related. Given the equivalent efficacy of atypical antipsychotics, weight-gain profile is a legitimate factor to consider when selecting a treatment (Nasrallah, Psychoneuroendocrinology. Vol 28, Suppl 1 pp 83-96, 2003; Homel, Casey and Allison Schizophrenia Research Vol 55(3) pp 277-284, 2002). This is the more relevant because obesity is commonly seen in patients with schizophrenia. According to some surveys the mean body mass index (BMI) for individuals with schizophrenia is significantly higher than individuals who are not schizophrenic (Homel, Casey and Allison, Schizophrenia Research, Vol 55(3) pp 277-284, 2002; Ananth et al Expert Review of Neurotherapeutics Vol 3(1) pp 59-68, 2003). Since overweight and obesity are risk factors for other health diseases, such as diabetes and cardiovascular disorders, the need for an improved drug treatment for individuals having both schizophrenia and overweight is clear.

It has now been found that treatment of such patients with asenapine is safer than treatment with just any one of most other antipsychotic agents.

The term treatment is used here to refer to a measure or set of measures taken and/or prescribed by a doctor in order to combat symptoms or consequences of disease. Treatment with a drug is by administration to the patient by any means known in the art directly to the patient or indirectly by prescription. The benefit of the improved treatment can be observed in individual patients, for example when switching to the new treatment from a treatment with any other antipsychotic agent with weight increasing side effect in that particular patient. The benefit can also be observed as a group effect, whereby it cannot be excluded that certain individuals still gain weight, but the overall group result definitely shows less average weight gain effect in comparison to a known treatment. In view of the favourable property of asenapine on weight it is an aspect of the invention to treat a patient for schizophrenia with asenapine, whereby the patient was having weight gain effect due to another antipsychotic agent. In this aspect of the invention the patient is not necessarily a patient with overweight. In another aspect, the need to avoid weight gain due to drug treatment is related to the special risk effect of overweight in that particular patient, for example due to the presence of other risk factors, for example for diabetes or cardiovascular disease. Such risk factors may stem from genetic disposition or behavioural habits, such as smoking. or sudden abstinence from smoking. It is therefore another aspect of the invention to treat a patient for schizophrenia with asenapine, whereby the patient needs to be protected against weight increase due to the presence of risk factors for a disease for which overweight is also a risk factor. Again such a patient in need of avoidance of weight increasing

effect is not necessarily already overweight. In still a further aspect the patient is in need of avoidance of weight increasing effect because of the presence of other weight increasing factors per se, such as abstinence from nicotine in relation to a decision to stop the smoking habit.

Schizophrenia is defined in the field of psychiatry as a disease falling in a specific diagnostic category with characteristic cognitive disturbances. Diagnosis can be made in accordance with the criteria given in handbooks for psychiatry, for example in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) published by the American Psychiatric Association, Washington, D.C. (1994).

Antipsychotic agent is a drug with therapeutic activity, be it curative or preventive, on patients with schizophrenia and other psychoses. In this description of the invention no difference is made in meaning between an antipsychotic drug, a neuroleptic drug and an antischizophrenia drug. In the art the terms are used interchangeably, although the term neuroleptic is usually avoided in modern times, since it is associated with the classic drugs having the strongest Parkinson-like side effects, resulting from uncompensated inhibition of dopaminergic neurotransmission in the brain.

Administration to a patient can be by any means aimed at making the drug available near the receptors in the body mediating the therapeutic effect. Tablets and capsules for oral intake are the most commonly known. For asenapine a sublingual formulation is developed so that the drug can be given in the oral cavity and is made available to the general circulation. See for example WO9523600

Obesity and overweight are used in the present context as obesity and overweight according to a judgment by a doctor, so that this term is used here with a medical meaning rather than with a meaning referring to (un)desirable physical appearance of people. Quantitative measures are defined in the art in order to have more objective criteria for overweight and obesity. A commonly used parameter is the body mass index (BMI) defined with the formula G/L^2; wherein G is body weight in kg and L is body height in meters. An acceptable BMI from the medical point of view is 25 kg/m^2. Higher values are considered overweight. Overweight as risk factor for other health problems is proportionally operative as such, that is, the higher the overweight, the higher the chance for emergence of other diseases, such as diabetes and cardiovascular disease. The World Health Organisation and the NIH have defined that the term obesity as a physical condition is characterised by a BMI of $\geq$ 30 kg/m^2. Note, for the purpose of clarity of terms that the term overweight includes the term obese, the latter being a more serious form of overweight. Since the effect of overweight is relative to the degree of overweight, different cut-off points than the mentioned 25 kg/m^2 are used to define unhealthy overweight. One can find in expert

literature values of 26 kg/m^2 and 27.3 kg/m^2 as starting criteria for obesity in women and 28 and 27.8 as starting criteria for obesity in men. The present invention has as further specific embodiments the use of asenapine for methods of treatment of schizophrenia in individuals with overweight defined objectively as those men selected with a BMI of ≥ 26, ≥ 26.5, ≥ 27, ≥ 27.3, ≥ 27.5, ≥ 28, ≥ 29, ≥ 30, ≥ 35 or ≥ 40 and/or those women selected with a BMI of ≥ 26, ≥ 26.5, ≥ 27, ≥ 27.5, ≥ 27.8, ≥ 28, ≥ 29, ≥ 30, ≥ 35 or ≥ 40.

Asenapine refers to the compound as registered by the WHO under that name, which is chemically named trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole. It is usually made available as the 1:1 maleate salt, so that asenapine may refer to the maleate salt specifically or to the base, or to any salt or hydrate of the base. In the present description the latter and broad meaning is used. The term encompasses also the separate enantiomeric forms of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, which can be used in pure form for the same purpose. When amounts of asenapine are given, reference is made to the base content of the substance, unless explicitly stated otherwise.

Asenapine is administered in an amount to the patient in a therapeutically effective amount. By a therapeutically effective amount is meant that amount which is capable of at least partially preventing, reversing, reducing, ameliorating or otherwise suppressing the psychotic disease being treated. The ultimate dosage to provide relief for the patient depends a.o. on individual characteristics, such as condition and age. A therapeutically effective amount can be determined by one of ordinary skill in the art using no more than routine experimentation.

Daily dose is the amount of drug administered per 24 hours in any pharmaceutical formulation. For extended release formulations the intended duration for effective dose administration is divided by the number of days in order to arrive at an indication of the daily dose of the treatment. Asenapine can effectively be used in the category of overweight patients in a daily dose range of 0.5 – 50 mg per person, whereby the exact amount is selected depending on route of administration, desired intensity of effect, and individual patient needs and tolerance. In particular the body weight can influence the daily dose, because portions of the drug may be stored in fat tissue, where it is temporarily not available for the receptors involved in the antischizophrenic effect. The preferred range for daily dose is 5-20 mg. Preferred is to administer the daily dose with a sublingual or buccal formulation in one or more dosage units (see WO 9523600) containing an amount of asenapine selected from the range of from 1- 15 mg, with preference for 5 or 10 mg.

It is an aspect of the invention to provide for the use of asenapine in a method for the manufacture of a medicine, which medicine comprises asenapine and is made to be suitable for the treatment of a patient with overweight, or a patient that was having weight gain effect due to another antipsychotic agent or a patient that needs to be protected against weight increase due to the presence of risk factors for a disease for which overweight is also a risk factor or due to the presence of other weight increasing factors.

In another aspect, the invention provides for a pharmaceutical formulation comprising asenapine suitable for the treatment of a patient with overweight, or a patient that was having weight gain effect due to another antipsychotic agent or a patient that needs to be protected against weight increase due to the presence of risk factors for a disease for which overweight is also a risk factor or due to the presence of other weight increasing factors.

Pharmaceutical formulations are commonly prescribed to the patient in "patient packs" containing a number dosing units or other means for administration of metered dose units for use during a distinct treatment period in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that it can be provided that the patient has access to a package insert contained in the patient pack. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions. Thus, the invention further includes a pharmaceutical formulation, as herein before described, in combination with packaging material suitable for said treatment. In such a patient pack the intended use of the formulation for the treatment according to the invention can be inferred by instructions, facilities, provisions, adaptations and/or other means to help using the formulation most suitably for the treatment. Such measures make a patient pack specifically suitable for and adapted for use for treatment according to the present invention.

Thus, the invention provides a patient pack for the treatment of a schizophrenia patient with overweight or at risk for overweight with asenapine. comprising means for administration of metered dose units in combination with packaging material suitable for said dose units, which patient pack comprises means to help a patient using the dose units most suitably.

Example

Assessment of the efficacy and safety of asenapine (5 mg twice a day) in subjects with acute exacerbation of their schizophrenic illness, compared to risperidone (3 mg twice daily and placebo in a randomized double blind, fixed-dose 6-week trial. The treatment period of 42 days consisted of a 21-day inpatient phase and a 21-day outpatient phase.

The study was done as a multicenter trial. Patients in the study were recruited in 27 centers and randomly assigned to one of the three trial groups.

Screening of candidate subjects for recruitment into the trial was done immediately after the informed consent was signed. The investigator or subinvestigator determined whether the subject met the DSM-IV criteria for schizophrenia. On day 0, the day before the first dose of trial medication was given, the health status of each subject was re-assessed to ensure eligibility for randomization of the subject in the trial. A total of 182 subjects were included into the trial, of these 180 received treatment: 59 asenapine, 59 risperidone, 62 placebo.

To be considered for inclusion in the trial, male or non-pregnant female subjects of 18 years of age or older and experiencing an acute exacerbation of their schizophrenic illness diagnosed according to DSM IV criteria with schizophrenia of the paranoid type [295.30], disorganised type [295.10], catatonic type [295.20], or undifferentiated type [295.90] were selected. Subjects were to have a PANSS score of at least 60 at baseline.

Asenapine and placebo were prepared as indistinguishable sublingual tablets according to WO9523600, example 1, with adaptation of the amount of asenapine in order to obtain proper amounts into the dosage units.

After a washout period of 3-7 days, subjects in the trial were randomized to the three treatment groups (asenapine, risperidone, placebo). Subjects randomized to the asenapine group received trial medication according to the following schedule: 1 mg twice daily on day 1, 2 mg twice daily on day 2, 3 mg twice daily on day 3, 4 mg twice daily on day 4, and 5 mg twice daily on days 5 through 42. Subjects randomized to the risperidone group received trial medication according to the following schedule: 1 mg twice daily on day 1, 2 mg twice daily on day 2, and 3 mg twice daily on days 3 through 42. Subjects randomized to the placebo group received placebo twice daily throughout the treatment period. Assessments during the treatment period were

conducted weekly, except for vital sign assessments during the inpatient phase which were conducted daily.

Among other tests the efficacy on disease symptoms is evaluated with the positive and negative syndrome scale (PANSS). Body weight was measured at screening and on day 42, or the subjects final day of treatment.

Demographic and other subject characterisation were performed and descriptive statistics were obtained for age, weight, and height by treatment group and pooled across treatment groups

Baseline characteristics by treatment group: age, weight, and height

		Asenapine 5 mg (N=59)	Risperidone 3 mg (N=59)	Placebo (N=62	Total (N=180)
Age(years)	N	59	59	62	180
	Median	39	41	41.5	41
	Maximum	70	61	68	70
	Minimum	21	22	22	21
Weight (kg)	N	57	58	58	173
	Median	84.40	82.25	84.15	83.60
	Maximum	155.0	161.9	150.0	161.9
	Minimum	58.6	57.2	54.9	54.9
Height (cm)	N	57	57	59	173
	Median	173	170	173	172
	Maximum	188	193	189	193
	Minimum	152	150	150	150
BMI*		28.20	28.46	28.12	28.26

* BMI was calculated with the median values of weight and height.

Results

Asenapine and risperidone were both significantly more effective than placebo in reducing the symptoms of schizophrenia. Clinically significant weight gain (i.e., an increase from baseline of ≥7%) was reported in 4% (N=2) of the asenapine subjects, 17% (N=8) of the risperidone-treated subjects, and 2% (N=1) of the placebo-treated subjects.

Table: Number of subjects with clinically significant change from baseline in body weight by treatment group (All-Subjects-Treated Group)

	Asenapine 5 mg			Risperidone 3 mg			Placebo		
	N	n	%	N	n	%	N	n	%
Increase of ≥ 7%	46	2	4.3	47	8	17.0	54	1	1.9
Decrease of ≥ 7%	46	0	0.0	47	1	2.1	54	4	7.4

N is total number of subjects with data and n is number of subjects in category

Of the 147 subjects in the All-Subjects-Treated Group who had weight data recorded at baseline and at the end of the trial, 11 had a clinically significant increase from baseline in body weight and 5 had a clinically significant decrease from baseline in

body weight. The percentage of subjects with clinically significant weight gain from baseline was highest in the risperidone group (17.0%), lower in the asenapine group (4.3%), and lowest in the placebo group (1.9%). Four subjects experienced a greater than 10% weight gain from baseline: 1 asenapine subject, 2 risperidone subjects, and 1 placebo subject.

At end point the risperidone group showed 1.9% increase in body weight from baseline, compared with a 0.5% increase of the asenapine group and a 0.3% increase for the placebo group.

Overall conclusion

The low incidence of clinically significant weight gain and minimal other side effects demonstrated that asenapine has a favorable benefit-risk profile.